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# Vision-Related Quality Of Life And Depression In Brazilian Patients With Toxoplasmic Retinochoroiditis

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ABSTRACT

*Purpose:* To investigate visual-related quality of life (VRQL) and prevalence and severity of depressive symptoms in Brazilian individuals with toxoplasmic retinochoroiditis (TRC).
*Design:* Comparative observational cross-sectional study. The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) and Beck Depression Inventory-II (BDI-II) were applied to respectively assess VRQL and depression in individuals consecutively seen at a uveitis referral center. Clinical/demographical data were collected. Descriptive/analytic statistics were employed, with $P<0.05$.
*Results:* Patients and controls were comparable concerning age, sex and socioeconomic level. VRQL scores for all subscales were significantly lower in TRC when compared with controls, particularly associated ($P<0.05$) with female sex, history of ≥2 prior TRC recurrences, concomitant use of systemic corticosteroids, monocular vision and blindness. Depressive symptoms were more prevalent in TRC (55/188; 29.2%) than in controls (34/182; 18.7%) ($P=0.023$), also being associated with lower VRQL scores ($P<0.001$). Seropositive and seronegative controls for toxoplasmosis had similar VRQL scores and comparable rates of depressive symptoms.
*Conclusion:* TRC affects VRQL in Brazilian individuals, particularly women, using systemic corticosteroids, with visual impairment and presenting recurrences of TRC. One-third of patients with TRC had evidence of depression, which was also associated with lower VRQL scores. Mental health issues in subjects with TRC should not be overlooked.



## INTRODUCTION

Up to one-third of the human population is infected with *Toxoplasma gondii*, with toxoplasmic retinochoroidits (TRC) being recognized as the main cause of infectious posterior uveitis worldwide. TRC manifests in up to 80% of individuals as congenital infection and in 2-20% as postnatally-acquired disease, also being a leading cause of low vision in endemic countries such as Brazil (De Paula et al., 2015; Vasconcelos-Santos, 2012). Few studies have addressed vision-related quality of life (VRQL) in individuals with TRC, with conflicting results (Peyron et al., 2011; De-La-Torre et al., 2011; Canamary et al., 2020). Pioneer studies on quality of life have suggested the inclusion of scales assessing factors such as anxiety and depression, which may interfere in quality of life perception (Ferraz et al., 2002). Even in individuals with treated ocular disorders, such as cataracts, a high prevalence of mental disorders has been associated with visual disability (Qian et al., 2012). This study aimed to investigate VRQL perception, and prevalence and severity of depressive symptoms in a large cohort of individuals with TRC consecutively seen at a university-based uveitis referral center in Brazil.

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## METHODS

The study adhered to the tenets of the Declaration of Helsinki and was prospectively approved by the institutional review board (Comitê de Ética em Pesquisa da UFMG-CAAE: 31060114.9.0000.5149).

### *Participants*

Individuals with TRC were consecutively recruited for 10 months at the uveitis unit of Hospital São Geraldo/Hospital das Clínicas, Universidade Federal de Minas Gerais, a university-based referral center in Belo Horizonte, Southeastern Brazil. All patients were aged ≥18 years, with a diagnosis of TRC established by a uveitis specialist (DVV-S), based on the presence of focal necrotizing retinochoroiditis with or without an associated retinochoroidal scar of variable pigmentation upon admission to the uveitis service. Positive serology (IgG) for toxoplasmosis and a favorable response (complete healing of TRC) following treatment with antiparasitic drugs ± systemic corticosteroids were also required (Holland, 2003; Vasconcelos-Santos, 2012). Laboratory investigation to rule out other etiologies such as syphilis and tuberculosis was also performed for all cases. Those cases with an uncertain diagnosis were not included.

Non-probability sampling included all patients with TRC matching the inclusion criteria. Controls were recruited from healthy individuals accompanying other patients seen at the eye hospital and hospital employees, not necessarily at the uveitis service, regardless of results of toxoplasma serology. The control group was matched by age, sex and socioeconomic level, in a proportion of one control for each case.

### *Design and procedures*

After informed consent, a single trained investigator (JSDA) interviewed all participants and applied the questionnaires. The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), a 25-question instrument that measures the impact of visual function in daily life activities of individuals with eye diseases, was used to assess VRQL perception. In addition to an overall composite score of VRQL (from 0-100), the NEI-VFQ-25 has 12 subscales assessing general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The instrument has been translated to the Portuguese language, with validation in the Brazilian population (Ferraz et al., 2002; Mangione et al., 2001; Mesquita Simão et al., 2008).

The Beck Depression Inventory II (BDI-II), a screening questionnaire comprising 21 questions, each one with four alternatives (weighing 0-3 points each) was used to determine prevalence and severity of depressive symptoms. The BDI-II total score of 0-13 corresponds to absence of depression, 14-19 to mild depression, 20-28 to moderate depression, and 29-63 to severe depression. A cutoff of >13 was considered as positive screening for depression, with reported sensitivity of 90% and specificity of 99% (Beck AT, Steer RA, 1996).

In addition, a data collection form was customized to obtain information relevant to this study, including demographic and clinical parameters, past medical and ocular history (including history of recurrences of TRC), and results of imaging and of laboratory investigations (including *T. gondii* serology, for individuals with TRC). Medical charts were also reviewed.

Peripheral blood was collected from control individuals, for serological testing with the Serion Elisa Classic *Toxoplasma gondii* IgG kit (Serion Gmbh, Würzburg, Germany). The sample was processed by a trained technician, following manufacturer's instructions.

All cases and controls underwent complete ophthalmological examination, consisting of assessment of best-corrected visual acuity (BCVA) on ETDRS (Early Treatment of Diabetic Retinopathy Study) chart, intraocular pressure (with Goldmann applanation tonometer), slit-lamp biomicroscopy, and fundus examination (indirect ophthalmoscopy). All accessible retinochoroidal lesions were documented by fundus photography. Fluorescein angiography and optical coherence tomography were also performed, when indicated.

Recurrence of TRC was defined as a new focus of retinochoroiditis (Holland, 2003; Vasconcelos-Santos, 2012), either in the previously affected eye or in the contralateral eye, with positive response to antiparasitic therapy. Retinochoroidal lesions were classified into macular or extra-macular, the latter when located outside the temporal vascular arcades. Blindness was defined in the setting of BVCA ≤20/200 in the better-seeing eye. Monocular vision was considered when BCVA was ≥20/63 in one eye and <20/200 in the contralateral eye. BCVA <20/400 was also converted to logMAR, as previously reported (Qian et al., 2012). Primary treatment of active retinochoroiditis at the center consists of classic therapy for 5 weeks with pyrimethamine (100 mg loading dose on the first day, followed by 25-50 mg daily), sulfadiazine (1 g every 6 h), folinic acid (5 mg daily), and prednisone (40 mg daily with progressive tapering). Other regimens include sulfamethoxazole/trimethoprim (for drug intolerance), and azithromycin or clindamycin (replacing sulfadiazine, for allergic patients).

### *Statistical analysis*

All data were tabulated in EpiData software version 3.1 (EpiData Association, Odense, Denmark). Internal consistency of NEI-VFQ-25 responses was verified using Cronbach's alpha coefficient. Statistical analyses were conducted using IBM SPSS Statistics 19 for Windows (IBM Corp., Armonk, NY). Data description included means, standard deviations, medians, and proportions. Associations and/or difference of proportions for categorical variables were assessed with Chi-square test. Medians were compared by Mann-Whitney test and correlations were assessed with Spearman coefficient. $P<0.05$ was regarded as statistically significant. The sample size was sufficient to detect a difference of up to 10 points in NEI-VFQ-25 between cases and controls, with a statistical power of 80% (alpha=0.05, two-tail).

## RESULTS

Among 418 individuals initially eligible for the study, 48 (11.5%) were excluded. Eighteen had past diagnosis of major psychiatric disorders and/or were using psychotropic drugs, 10 were immunosuppressed, six had other ocular diseases, and two had no VA testing. Between controls, five had BCVA <20/63 and seven were excluded because of previously undetected retinochoroidal scars suggestive of TRC in the presence of IgG antibodies to *T. gondii*. (Figure 1). These latter individuals had denied any ocular problem in their past medical history.

Of the 370 participants eventually included in the study, 188 were patients with TRC (50.8%) and 182 were healthy controls (49.2%). The age of participants varied between 18-82 years (median: 33); 204 were male (55.1%) and 201 were mulattos (54.3%). Ninety-eight/176 controls (55.7%) and all cases of TRC were seropositive for toxoplasmosis. Both groups were comparable regarding age (P=0.782), sex (P=0.835) and socioeconomic level (P=0.522).

Among patients with TRC, 33.5% (63/188) had BCVA <20/200 in at least one eye, with 5.9% (11/188) having BCVA <20/200 in one

**Table 1**
Comparison of NEI-VFQ-25[a] scores between individuals with toxoplasmic retinochoroiditis and controls.

| Variables | No. responses | Mean score | 95% CI | Median score | CV | SD | P-value[b] |
|---|---|---|---|---|---|---|---|
| General health (370) | Cases (188) | 53.46 | 49.98-56.93 | 50.00 | 0.45 | 24.14 | **<0.001** |
| | Controls (182) | 72.25 | 68.63-75.88 | 75.00 | 0.34 | 24.78 | |
| General vision (370) | Cases (188) | 57.66 | 55.07-60.25 | 60.00 | 0.31 | 17.99 | **<0.001** |
| | Controls (182) | 84.07 | 81.71-86.42 | 80.00 | 0.19 | 16.11 | |
| Ocular pain (370) | Cases (188) | 77.12 | 73.68-80.58 | 87.50 | 0.31 | 23.98 | **<0.001** |
| | Controls (182) | 92.79 | 90.89-94.68 | 100.00 | 0.14 | 12.96 | |
| Near activities (370) | Cases (188) | 75.53 | 72.97-78.97 | 83.33 | 0.32 | 23.89 | **<0.001** |
| | Controls (182) | 95.10 | 93.62-96.58 | 100.00 | 0.11 | 10.10 | |
| Distance activities (370) | Cases (188) | 77.84 | 74.47-81.20 | 83.33 | 0.30 | 23.38 | **<0.001** |
| | Controls (182) | 95.56 | 94.16-96.96 | 100.00 | 0.10 | 9.54 | |
| Social functioning (370) | Cases (188) | 94.45 | 92.06-96.77 | 100.00 | 0.17 | 16.36 | **<0.001** |
| | Controls (182) | 99.86 | 99.67-100.05 | 100.00 | 0.01 | 1.31 | |
| Mental health (370) | Cases (188) | 64.09 | 60.88-67.31 | 68.75 | 0.35 | 22.31 | **<0.001** |
| | Controls (182) | 93.37 | 92.02-94.73 | 93.75 | 0.10 | 9.25 | |
| Role difficulties (370) | Cases (188) | 76.93 | 72.70-81.16 | 87.50 | 0.38 | 29.40 | **<0.001** |
| | Controls (182) | 96.64 | 95.17-98.10 | 100.00 | 0.10 | 9.99 | |
| Dependency (370) | Cases (188) | 84.22 | 80.59-87.85 | 100.00 | 0.30 | 25.26 | **<0.001** |
| | Controls (182) | 99.31 | 98.91-99.72 | 100.00 | 0.03 | 2.75 | |
| Driving (196) | Cases (92) | 83.42 | 79.49-87.36 | 87.50 | 0.23 | 19.00 | **<0.001** |
| | Controls (104) | 93.15 | 91.12-95.18 | 100.00 | 0.11 | 10.43 | |
| Color vision (370) | Cases (188) | 95.35 | 93.30-97.39 | 100.00 | 0.15 | 14.21 | **0.011** |
| | Controls (182) | 98.63 | 97.71-99.55 | 100.00 | 0.07 | 6.89 | |
| Peripheral vision (370) | Cases (188) | 78.86 | 75.00-82.71 | 100.00 | 0.34 | 26.77 | **<0.001** |
| | Controls (182) | 99.18 | 98.52-99.83 | 100.00 | 0.05 | 4.48 | |
| **TOTAL SCORE** (370) | Cases (188) | 77.73 | 75.29-80.16 | 81.80 | 0.22 | 16.91 | **<0.001** |
| | Controls (182) | 95.30 | 94.53-96.07 | 96.48 | 0.06 | 5.25 | |

CV: coefficient of variation SD: standard deviation
**P-value (Mann-Whitney test); $\alpha$= P<0.05
[a] NEI-VFQ-25: 25-Item National Eye Institute Visual Function Questionnaire

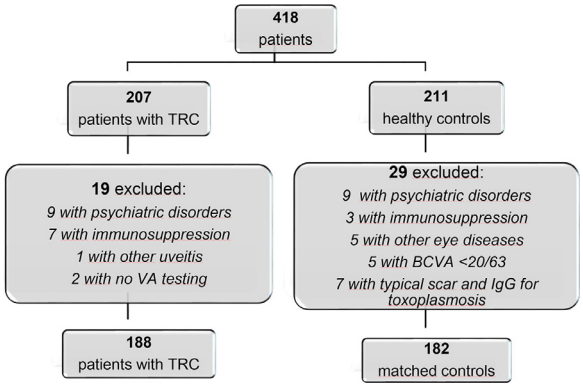


**Figure 1.** Flow diagram illustrating included and excluded cases and controls.

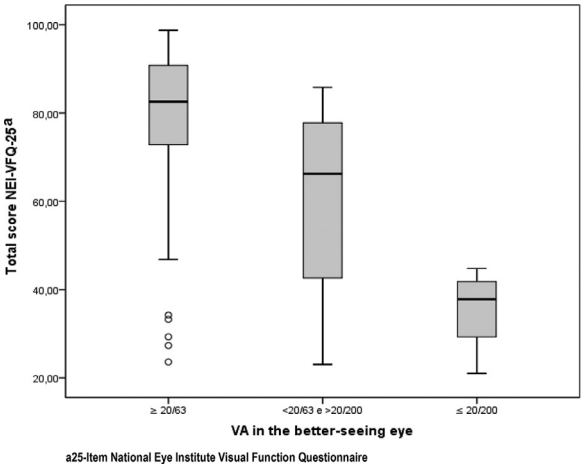


**Figure 2.** VIsion-related quality of life scores (NEI-VFQ-25[a]) according to visual acuity in patients with toxoplasmic retinochoroiditis.

eye and low vision in the contralateral eye and 27.7% (52/188) being characterized with monocular vision. At the time of VRQL assessment, active retinochoroiditis was evidenced in 52.1% (98/188) and 179 patients with TRC (95.2%) had retinochoroidal scar(s) in either eye. Retinochoroidal involvement was bilateral in 29.8% (56/188) and macular in 31.4% (59/188). Previous recurrences of TRC were reported by 100 patients (53.2%), with 87 having ≥2 and 13 (6.4%) having ≥4 recurrences. Mean follow-up at the uveitis unit ranged from 0-21 years (mean, 21.07 ± 40.03 months; median, 1 month), 67.4% had <12 months of follow-up. As for drug therapy, 114 (60.6) were on classic treatment, 105 (55.9%) were using prednisone, and eight (4.4%) were using sulfamethoxazole-trimethoprim.

NEI-VFQ-25 scores were significantly lower for patients with TRC than for controls in all subscales and also in total score (Table 1). Internal consistency was acceptable for all subscales of NEI-VFQ-25, including ocular pain ($\alpha$=0.626), near activities ($\alpha$=0.771), distance activities ($\alpha$=0.756), social functioning ($\alpha$=0.761), mental health ($\alpha$=0.744), role difficulties ($\alpha$=0.745), dependency ($\alpha$=0.828), and driving ($\alpha$=0.819). Factors associated with worse VRQL scores in individuals with TRC included female sex (P=0.003), history of ≥2 recurrences (P=0.022), and concomitant use of systemic corticosteroids (P=0.007). In addition, patients with BCVA <20/200 in at least one eye (P<0.001), including those with monocular vision (P=0.009) and blindness (P<0.001), also had worse VRQL scores (Table 2**)**. BCVA (logMAR) in the better-seeing eye was inversely associated with VRQL score (Figure 2). There was no correlation (-0.059, P=0.418) between follow-up time and VRQL scores.

When analyzing BDI-II results, scores consistent with depression were more prevalent in patients with TRC (55/188; 29.2%) than in controls (34/182; 18.7%; P=0.020). Regarding severity of depressive symptoms, 21/188 patients with TRC (11.2%) had BDI-II scores consistent with mild depression, 25/188 (13.3%) with mod-

**Table 2**
Characterization of individuals with retinochoroiditis according to the scores of vision-related quality of life (NEI-VFQ-25[a]).

| Variables | No. responses | Mean score | CI 95% | Median score | CV | SD | P-value[b] |
|---|---|---|---|---|---|---|---|
| Gender (188) | Female (83) | 74.91 | 71.36-78.46 | 76.48 | 0.22 | 16.26 | **0.003** |
| | Male (105) | 79.96 | 76.64-83.28 | 84.24 | 0.21 | 17.16 | |
| Active retinochoroiditis (188) | Yes (98) | 77.36 | 74.44-80.27 | 80.61 | 0.19 | 14.53 | 0.095 |
| | No (90) | 78.54 | 74.54-82.53 | 83.37 | 0.24 | 18.96 | |
| Retinochoroidal scars (188) | Yes (180) | 77.67 | 75.18-80.16 | 81.83 | 0.22 | 16.89 | 0.325 |
| | No (8) | 83.57 | 72.81-94.33 | 85.38 | 0.15 | 12.87 | |
| Bilateral involvement (188) | Yes (57) | 75.66 | 70.65-80.67 | 80.94 | 0.25 | 18.70 | 0.478 |
| | No (131) | 78.89 | 76.15-81.62 | 82.42 | 0.20 | 15.82 | |
| Macular involvement (188) | Yes (60) | 74.96 | 70.11-79.80 | 80.00 | 0.25 | 18.57 | 0.135 |
| | No (128) | 79.28 | 76.53-82.04 | 83.67 | 0.20 | 15.67 | |
| Prior recurrences of retinochoroiditis (188) | Yes (100) | 74.72 | 70.72-78.44 | 80.09 | 0.25 | 18.76 | **0.022** |
| | No (88) | 81.15 | 78.21-84.08 | 84.81 | 0.17 | 13.85 | |
| Number of prior recurrences (188) | No recurrence (89) | 81.10 | 78.06-83.98 | 84.24 | 0.17 | 13.87 | 0.070[c] |
| | 2-3 recurrences (87) | 75.32 | 71.33-79.32 | 80.64 | 0.25 | 18.75 | |
| | >3 recurrences (12) | 71.18 | 58.70-83.66 | 72.96 | 0.28 | 19.64 | |
| Current use of systemic corticosteroids (188) | Yes (105) | 76.14 | 73.12-79.16 | 78.17 | 0.20 | 15.59 | **0.007** |
| | No (83) | 79.74 | 75.73-83.74 | 85.29 | 0.23 | 18.34 | |
| Side-effects of antitoxoplasmic treatment (188) | Yes (77) | 75.11 | 71.16-79.05 | 78.86 | 0.23 | 17.39 | **0.037** |
| | No (111) | 79.55 | 76.46-82.64 | 83.67 | 0.21 | 16.40 | |
| BCVA ≤20/200 in the better-seeing eye (188) | Yes (5) | 34.94 | 22.87-47.01 | 37.83 | 0.28 | 9.72 | **<0.001** |
| | No (183) | 78.90 | 76.64-81.16 | 81.86 | 0.20 | 15.43 | |
| BCVA <20/200 in at least one eye (188) | Yes (63) | 68.91 | 63.80-74.03 | 74.00 | 0.30 | 20.33 | **<0.001** |
| | No (127) | 82.17 | 79.89-84.45 | 85.79 | 0.16 | 12.86 | |
| Monocular vision (188) | Yes (52) | 73.01 | 67.98-78.05 | 76.46 | 0.25 | 18.08 | **0.009** |
| | No (136) | 79.53 | 76.79-82.77 | 84.28 | 0.20 | 16.15 | |

CV: coefficient of variation; SD: standard deviation; BCVA: best-corrected visual acuity
[a] NEI-VFQ-25: 25-Item National Eye Institute Visual Function Questionnaire
[b] p (Mann-Whitney test)
[c] p (Kruskal-Wallis test); $\alpha$=p<0.05

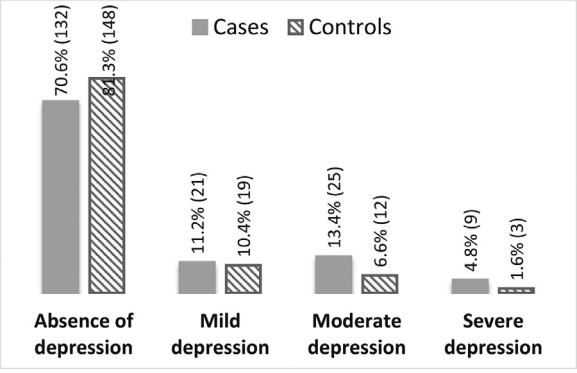


**Figure 3.** Comparison of severity of depressive symptoms between individuals with toxoplasmic retinochoroiditis and controls, according to Beck Depression Inventory II scales.

erate depression, and 9/188 (4.8%) with severe depression. Among the 182 controls, scores consistent with mild, moderate, and severe depression were respectively disclosed in 19 (10.4%),12 (6.6%), and 3 (1.6%) individuals, with this difference being statistically significant (P=0.036). As expected, patients screening positive for depression on BDI-II had lower VRQL scores on NEI-VFQ-25 (P<0.001). Even though these scores were progressively lower for more severe depression strata (Figure 3), this difference was not statistically significant.

Among controls, there was no difference in VRQL scores between *T. gondii* seropositive and seronegative individuals (P=0.981). Seropositivity was also not associated with depressive symptoms in those individuals (P=0.399) (Table 3).

## DISCUSSION

This study confirms the hypothesis that ocular toxoplasmosis influences the perception of vision-related quality of life (VRQL) of affected Brazilian individuals. Depressive symptoms were also more prevalent in these individuals. It is known that individuals with marked visual impairment have quality of life scores comparable with those of patients with severe conditions, including peptic ulcer disease, severe angina pectoris, and even stroke (Brown et al., 2003). These results may lay the ground for development/improvement of integrative interventions for individuals with ocular toxoplasmosis.

High prevalence of toxoplasmic infection has been associated with increased prevalence of ocular disease (Khan et al., 2005). Seroprevalence of toxoplasmosis in the current control group was as high as 53.8%, with seven individuals of those with chronic *T. gondii* infection displaying retinochoroidal lesions consistent with toxoplasmosis and being subsequently excluded for comparison in the control group. These numbers are significantly higher than in most studies from Europe and North America (Holland, 2003; Kijlstra and Petersen, 2014), and comparable with numbers found in Colombia, in line with greater prevalence/severity of ocular toxoplasmosis in South America (De-La-Torre et al., 2009). Interestingly, these individuals with retinochoroidal lesions were unaware of their serological status and of the presence of the retinochoroidal scars, as the clear majority was unilateral and peripheral.

Previous studies have demonstrated the impact of uveitis in general health and quality of life of affected individuals (Schiffman RM, Jacobsen G, 2001). In addition to compromised VRQL, increased prevalence of depression has also been observed in patients with noninfectious uveitis (Qian et al., 2012). Infectious uveitis like toxoplasmosis, however, has not been sufficiently investigated. A French study did not find a significant impact of congenital toxoplasmosis on quality of life, but all patients had previously been treated pre-and postnatally, and only a small number (12.7%) eventually developed visual impairment (Peyron et al., 2011). Another small study from Colombia disclosed the association of ocular toxoplasmosis with worse VRQL, but only 29 individuals with toxoplasmosis were analyzed (De-La-Torre et al., 2011). A recent study in another referral center in Southeastern Brazil confirmed

**Table 3**
Global scores of vision-related quality of life (NEI-VFQ-25[a]) and of depressive symptoms (BDI-II[b]) among healthy controls seropositive and seronegative for toxoplasmosis.

| | Variables | No. responses | Mean | CI 95% | Median | CV | SD | P-value[c] |
|---|---|---|---|---|---|---|---|---|
| VRQL | Serum IgG for toxoplasmosis | No (78) | 95.27 | 94.04-96.51 | 96.57 | 0.06 | 5.47 | 0.931 |
| | | Yes (98) | 95.38 | 94.39-96.37 | 96.48 | 0.05 | 4.95 | |
| Depressive symptoms | Serum IgG for toxoplasmosis | No (78) | 7.18 | 5.55-8.81 | 5.00 | 1.00 | 7.21 | 0.399 |
| | | Yes (98) | 7.86 | 6.41-9.30 | 5.50 | 0.92 | 7.20 | |

VRQL: Visual-related quality of life
[a] NEI-VFQ-25: 25-item National Eye Institute Visual Function Questionnaire
[b] BDI-II: Beck Depression Inventory II
[c] p (Mann-Whitney test); $\alpha$ $p<0.05$

this finding, but also with a relatively small number of patients and without a control group. VRQL findings were associated with impaired vision, but not with other clinical characteristics of the disease. A high prevalence of anxiety and of depression symptoms was also found (Canamary et al., 2020).

The current study found that VRQL scores were significant lower in patients with TRC when compared with controls, and this difference was found not only in total score, but also in all NEI-VFQ-25 subscales. Macular involvement was seen in 30.3% of the current patients, with BCVA <20/200 being disclosed in 33.5%. Recurrences of TRC were also very commonly reported (53.2%). This increased severity of ocular toxoplasmosis, as generally observed in Brazil and other South American countries, may have partly accounted for the impact on VRQL perception.

Factors associated with worse VRQL in individuals with uveitis have been investigated; these have included worse visual acuity, disease activity, intensive therapy, number of comorbidities, and unemployment status (Schiffman RM, Jacobsen G, 2001). Depression has also been associated with lower VRQL scores in individuals with noninfectious uveitis (Qian et al., 2012) and in patients with active uveitis (Onal et al., 2018). The Colombian study found that decreased VRQL was associated with bilateral lesions and with recurrences of TRC (De-La-Torre et al., 2011). In patients with non-infectious uveitis, presence of ocular pain had a profound impact on several aspects of quality of life (Verhagen et al., 2018). Worse VRQL scores were found in patients with: female sex (P=0.003), ≥2 recurrences of TRC (P=0.022), monocular vision (P=0.009), BCVA <20/200 (P<0.001), and positive screening for depression (P<0.001). An unexpected finding was the lack of association between VRQL and bilateral (P=0.478) and active lesions (P=0.095). Conversely, individuals on systemic corticosteroids for treatment of active TRC had worse VRQL scores (P=0.007). Among patients screened with depressive symptoms, VRQL scores were also significantly lower (P<0.001). This had been observed in patients with noninfectious uveitis, but not yet in the context of ocular toxoplasmosis (Qian et al., 2012).

Interestingly, a 16.3-point difference in NEI-VFQ-25 total score was found between depressed and non-depressed individuals. This difference was higher than the 11.2 points found in patients with age-related macular degeneration (Brody et al., 2001), 12.8 points found in visual-disabled Latinos (Luo, 2004), 13 points found in patients with active uveitis (Onal et al., 2018), and close to 15.5 points disclosed in individuals with retinitis pigmentosa (Hahm et al., 2008). However, it was lower than the 22 points previously found in patients with noninfectious uveitis (Qian et al., 2012).

Prevalence of depression was also higher in individuals with TRC (29.1%) than in controls (18.6%) in the current study, and comparable with the prevalence in patients with noninfectious uveitis (26.4%) (Qian et al., 2012). It was also superior to the lifelong estimate of 18.7% (Bromet et al., 2011) and also to the prevalence in another smaller study on ocular toxoplasmosis in São Paulo, Brazil (19%) (Canamary et al., 2020). Yet, the current rates are substantially higher that the ones observed in patients with ocular inflammatory disease in Thailand (8.1%). This study found that higher scores of anxiety and depression were associated with poorer levels of understanding of ocular inflammatory disease and poor self-reported visual function (Sittivarakul and Wongkot, 2019). In another population-based study, *T. gondii* antibodies were not associated with major depression, but were associated with type I bipolar disorder with both manic and depressive features (Pearce et al., 2012). In the current study, prevalence of moderate and severe depression in patients with TRC was respectively twice and three times higher than in controls. This may be related to anxiety underlying the ocular problem and fear of recurrences and of visual disability, particularly in the context of a uveitis referral center concentrating on more severe cases. Use of systemic corticosteroids for the management of active TRC may also be another contributing factor. These results suggest that mental health issues should not be overlooked in these individuals.

An increasing number of studies have also been challenging the concept that *T. gondii* infection is benign and asymptomatic in most patients, suggesting the association of toxoplasmosis with several neuropsychiatric disorders (de Barros et al., 2017). Biological mechanisms underlying this possible association are not completely understood, but may be related to parasite replication in the CNS, with tropism to areas of the limbic system and subsequent changes to local biosynthesis of neurotransmitters such as dopamine, serotonin and norepinephrine (Flegr, 2013; Hurley et al., 2012; Ling et al., 2011). The current study found no significant difference in VRQL (P=0.981) and depressive symptoms (P=0.399) between seropositive and seronegative control individuals. This result is consistent with a recent meta-analysis on association of toxoplasmic infection with neuropsychiatric disorders in humans. After scrutinizing 50 studies, the authors identified and association of chronic *T. gondii* infection with schizophrenia (OR=1.81; P<0.00001), bipolar disorder (OR=1.52; P=0.02), obsessive-compulsive disorder (OR=3.4; P<0.001), and addiction (OR=1.91; P<0.00001), but not with major depression (OR=1.21; P=0.28) (Gale et al., 2014). A large population-based study with 1846 young adults also did not find any significant association between seropositivity to *T. gondii* and major depressive disorder, generalized anxiety disorder or panic disorder (de Bles et al., 2021). Another cohort study with 837 individuals followed since birth found only marginal evidence of increased suicidal behavior in seropositive individuals, without significant risk of other major psychiatric disorders (Sugden et al., 2016).

Ocular toxoplasmosis is recognized as more severe and more prevalent in Brazil than in Europe and other parts of the world, being a public health problem. However, it is still uncertain whether this is attributable to more virulent strains of the parasite and/or to genetic factors of the host. In addition, increased exposure rate in the environment may also be implicated. Therefore, the current findings should be interpreted and extrapolated with cau-

tion (Khan et al., 2006; Peyron and Wallon, 2011; Vasconcelos-Santos and Queiroz-Andrade, 2011).

Limitations of this study included its cross-sectional design, allowing identification of associations but not inference of causality (Hayman et al., 2007). Moreover, depressive symptoms were assessed with BDI-II, a self-reported questionnaire, but not through a comprehensive psychiatric assessment (De Oliveira et al., 2011). Finally, being a referral center in Brazil, more severe cases of TRC are to be expected, limiting the extrapolation of the findings. Despite these limitations, the large sample, including a random case mix of TRC (recently diagnosed individuals, as well as those with longstanding ocular disease and multiple recurrences) is likely representative of immunocompetent adults with ocular toxoplasmosis in Brazil.

In conclusion, ocular toxoplasmosis significantly affects VRQL in Brazilian individuals, particularly women, using systemic corticosteroids, with significant visual impairment and presenting recurrences of TRC. Nearly one-third of patients with TRC had evidence of depression, which was also associated with lower VRQL scores. Mental health issues should not be overlooked in individuals with ocular toxoplasmosis and may deserve further investigation in larger longitudinal studies.

## Declaration of Competing Interests

None declared.

## Ethical approval

This study was approved by the institutional review board (Comitê de Ética em Pesquisa da UFMG, CAAE no. 31060114.9.0000.5149), following the tenets of the Declaration of Helsinki. Signed informed consent was obtained from all participants.

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## Contributors

Conceptualization, methodology and investigation: JSDA and DVVS. Serological analysis of controls: JSDA and SC. Formal analysis: JSDA and JDT. Drafting the work and revising it critically for important intellectual content: all authors. Final approval of the version to be published: all authors.

## Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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